REMARKS

Further examination of claims 1, 2, 6-10, and 14-16 is reported in the present, final Office Action. Claims 1, 2, 6-10, and 14-16 remain provisionally rejected under 35 U.S.C. § 101; claims 9, 10, and 14-16 remain rejected under 35 U.S.C. § 112, first paragraph; and claims 1, 2, 6-10, and 14-16 remain rejected under 35 U.S.C. § 102 or 35 U.S.C. § 103(a).

Applicants respectfully submit that, in the interest of expediting prosecution, each of the rejections has been addressed in a manner that is consistent with what appears may be acceptable to the Examiner to render the present claims allowable. Applicants thus respectfully request reconsideration of the present claims and, if possible, ask that the Examiner contact the undersigned by telephone in the event that the next Office Action is not a Notice of Allowance. Each of the rejections is addressed as follows.

Provisional Rejection under 35 U.S.C. § 101

Claims 1, 2, 6-10, and 14-16 were provisionally rejected under § 101 as claiming the same invention as claims 1, 2, 6, 7, 9-11, and 15-18 of co-pending application serial no. 09/152,638. When the only rejection remaining in a case is a provisional double patenting rejection, an application should be allowed to issue. M.P.E.P. § 822.01. In view of the amendment and remarks provided in this reply, applicants submit that all of the grounds of rejection in this case, other than the provisional double patenting rejection, have been met. Accordingly, the double patenting rejection should be withdrawn and the case allowed to issue.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 9, 10, and 14-16 were rejected under 35 U.S.C. § 112, first paragraph, with the Examiner stating that the specification does not reasonably enable the therapeutic/prophylactic use of any chimeric flavivirus other than YF/JE SA14-14-2 or YF/JE Nakayama, nor the use of such chimeras against any infection other than Japanese encephalitis virus infection. This rejection has been met by the present amendment to these claims to specify that which the Examiner has deemed enabled: use of YF/JE SA14-14-2 or YF/JE Nakayama chimeras in the prevention or treatment of Japanese encephalitis virus infection. Applicants thus respectfully request that this rejection be withdrawn. Applicants also note that they reserve the right to pursue the original or similar claims in future applications.

Rejections under 35 U.S.C. §§ 102 and 103(a)

Claims 1, 2, 6-10, and 14-16 remain rejected under § 102(b) as being anticipated by, or, alternatively, under § 103 for obviousness over, Lai et al., WO 93/06214. This rejection is respectfully traversed.

In response to applicants' previous submission, the Examiner stated that the feature upon which applicants relied in making their argument (i.e., that the capsid protein in the claimed chimeras is from yellow fever virus), is not present in the rejected claims. This concern has been met by the present amendments to claims 1 and 9, from which the other rejected claims depend, which now specify that the capsid proteins in the chimeras of these claims are from yellow fever virus. Thus, the present claims are drawn to a very specific type of chimera, including the non-structural and capsid proteins of a yellow fever virus and the prM and E proteins of another

flavivirus. The cited Lai PCT publication does not describe or render obvious such chimeras, for the reasons discussed in applicants' previous replies, which are set forth again below.

The focus of the Lai PCT publication is chimeras that include structural proteins from tick-borne encephalitis virus and non-structural proteins of dengue virus, as well as intertypic dengue chimeras. In most of the chimeras described in the Lai publication, all three structural proteins (capsid, pre-membrane, and envelope) of one flavivirus are replaced with those of another. In the only two specific examples of chimeras including non-structural and capsid proteins from a first virus and pre-membrane and envelope proteins from another virus, dengue virus is employed as the source of non-structural and capsid proteins. The pre-membrane and envelope proteins in these chimeras are from tick-borne encephalitis virus (page 23, lines 10-14) and Japanese encephalitis virus (page 5, line 31 through page 6, line 2). The Lai publication notes that the production of this type of chimera, having only two structural proteins replaced, was unexpected (page 21, lines 24-33), and does not suggest that such chimeras be made using other flaviviruses, such as yellow fever virus, as the source of non-structural and capsid proteins, as is required for the chimeras of the present claims. Indeed, the only context in which yellow fever virus is mentioned in the Lai publication is in the context of a chimera in which the sources of all structural and all non-structural proteins are different. For example, at page 14, lines 25-31, the Lai publication states that the invention "relates to a chimeric virus comprising: 1) a non-structural region of... yellow fever virus... and 2) a structural region selected from [list of flaviviruses] wherein the structural region is from a different "type" of dengue virus or flavivirus than the non-structural region." Thus, because the Lai publication does not describe a yellow fever-based chimera that includes the non-structural and capsid proteins of yellow fever virus and

the pre-membrane and envelope proteins of another flavivirus, as is required by the present claims, applicants respectfully request that the rejection under § 102(b) be withdrawn.

Applicants also request that the rejection under § 103(a) be withdrawn, for the same reasons stated in applicants' previous replies. In particular, as is noted above, the Lai publication makes note of only two chimeras including non-structural and capsid proteins from a first virus and pre-membrane and envelope proteins from another virus: dengue virus is employed as the source of non-structural and capsid proteins, and the pre-membrane and envelope proteins in these chimeras are from tick-borne encephalitis virus or Japanese encephalitis virus. These chimeras are similar to those that were referred to in the Venugopal reference, as discussed applicants' previous replies. Venugopal, at page 972, left column, citation 113, referred to a paper by Pletnev et al. (Proc. Natl. Acad. Sci. U.S.A. 89:10532-10536, 1992; a copy was enclosed with applicants' April 19, 2002 reply) as describing a chimera that is a dengue virus type 4-based vector into which tick-borne encephalitis (TBE) virus prM and E proteins were inserted). In this vector, however, not only were the prM and E proteins of TBE inserted into the dengue vector, but also the TBE signal sequence that lies between the C and prM proteins was inserted in place of the corresponding dengue sequence (see the first construct in the Figure enclosed with applicants' April 19, 2002 reply ("construct 1"), which is described in further detail below). The same is true for the dengue/TBE and dengue/JE chimeras described in the Lai publication, on which Pletnev is named as an inventor.

As was stated in applicants' previous replies, when this approach, involving the insertion of signal, prM, and E sequences of one virus into another, was used with yellow fever virus as the backbone and dengue virus as providing the inserted signal sequence and structural proteins,

it was unsuccessful in the production of a viable chimera. This is shown, for example, in the paper by Galler et al. (Brazilian Journal of Medical and Biological Research 30:157-168, 1997) that was enclosed with applicants' April 19, 2002 reply. In particular, on page 164, second column, Galler states that when sequences of the prM/M/E proteins of two dengue virus strains, PR159/S1 and New Guinea C, were inserted into yellow fever virus in place of the corresponding yellow fever proteins, "all attempts to recover the chimeric virus with either PR159/S1 or New Guinea C cDNA failed (Galler R and Ferreira II, unpublished data), suggesting the impracticability of this approach" (emphasis added). (Also see construct 2 in the Figure enclosed with applicants' April 19, 2002 reply, and Caufour et al., Virus Res. 79:1-14, 2001 (a copy was enclosed with applicants' April 19, 2002 reply).) Thus, the method of the prior art was not successful when used in the context of a yellow fever virus backbone and, moreover, the art clearly taught away from the practicability of such an approach.

Applicants, as was discussed in their previous replies, determined why the prior art method failed, and discovered a way to overcome this obstacle and make viable yellow fever-based chimeras. In particular, applicants determined that using a signal sequence having the length of that of the yellow fever virus backbone was important to enable proper processing of the polyprotein, leading to the production of viable chimeric virus. In the case of the failed dengue/yellow fever chimera mentioned above (construct 2 of the Figure enclosed with applicants' April 19, 2002 reply), the 14 amino acid dengue signal sequence was used. When applicants instead used the 20 amino acid yellow fever sequence, they obtained a viable yellow fever/dengue chimera (construct 4 of the Figure). As is discussed above, this method has also been successful with yellow fever-based chimeras including inserts from other dengue types,

Japanese Encephalitis virus (construct 3), and West Nile virus.

A reason for this difference is shown in the Figure, which illustrates the structural polyproteins of different chimeric constructs as they pass through the endoplasmic reticulum (ER) membrane during proteolytic processing. The first construct, which includes the Tick-borne Encephalitis virus prM, E, and signal sequences and Dengue virus C and backbone sequences, is positioned in the membrane such that cleavage of the signal sequence, which spans the membrane, can occur on each side of the membrane (arrowheads), leading to the production of viable virus. This construct corresponds to that described by Lai, as is mentioned above.

The second construct was made in the same manner as the first, but included the Dengue (rather than TBE) virus prM, E, and signal sequences and Yellow fever (rather than Dengue) virus C and backbone sequences. As is illustrated in the Figure, the signal sequence of this construct is not positioned in such a way as to facilitate cleavage on both ends, which are each embedded in the ER membrane. Thus, this construct failed to lead to the production of viable virus.

The third and fourth constructs were made using the methods of the present invention, and include the PrM and E sequences of the insert virus (Japanese encephalitis virus and Dengue virus, respectively), and the Yellow Fever virus signal, C, and backbone sequences. As is illustrated in the Figure, the signal sequences of these constructs are positioned so as to facilitate proteolytic processing, enabling the production of viable virus.

Thus, use of the prior art methods (i.e., the method of Lai) to make yellow fever-based chimeras failed, and it took the discovery of applicants, relating to the C/prM signal sequence, to enable the production of such chimeras. Neither this obstacle, nor the manner in which it was

overcome, would have been obvious to those of skill in this art at the time of applicants' invention.

Thus, because the art did not suggest the claimed invention and, moreover, because the art taught away from the invention, applicants thus submit that the rejection of the present claims under §§ 102(b) and 103(a) should be withdrawn.

Claims 1, 2, 6-10, and 14-16 also remain rejected under § 102(e) as being anticipated by, or, alternatively, under § 103(a) for obviousness over, Lai et al., U.S. Patent No. 6,184,024. This rejection is respectfully traversed.

Similar to the rejection over the Lai PCT publication, in response to applicants' previous submission concerning the Lai patent, the Examiner stated that the feature upon which applicants relied in making their argument (i.e., that the capsid protein in the claimed chimeras is from yellow fever virus), is not present in the rejected claims. As is discussed above, this concern has been met by the present amendments to claims 1 and 9, from which the other rejected claims depend, which specify that the capsid proteins in the chimeras of these claims are from yellow fever virus. The present claims therefore are drawn to a specific type of chimera, including the non-structural and capsid proteins of a yellow fever virus and the prM and E proteins of another flavivirus. The cited Lai patent does not describe or render obvious such specific chimeras, for the reasons discussed in applicants' previous replies, which are set forth again below.

Similar to the Lai PCT publication discussed above, the Lai patent does not describe chimeras including non-structural and capsid proteins of yellow fever virus and pre-membrane and envelope proteins of other flaviviruses, as required by the present claims. Rather, the focus of the Lai patent is chimeras that include all three structural proteins (capsid, pre-membrane, and

envelope) of one flavivirus replaced with those of another. Similar to the Lai PCT publication, the only two specific examples of chimeras including non-structural and capsid proteins from a first virus and pre-membrane and envelope proteins from another virus, dengue virus is employed as the source of non-structural and capsid proteins. The pre-membrane and envelope proteins in these chimeras are from tick-borne encephalitis virus (column 19, lines 55-58) and Japanese encephalitis virus (column 25, lines 1-7). The Lai patent does not even suggest that such chimeras be made using yellow fever virus as the source of non-structural and capsid proteins, as is required by the present claims. Indeed, the only context in which yellow fever virus is mentioned in the Lai patent is in the context of a chimera in which the sources of all structural and all non-structural proteins are different. For example, at column 13, lines 21-31 the Lai publication states that the invention "relates to a chimeric virus comprising: 1) a non-structural region of... yellow fever virus... and 2) a structural region selected from [list of flaviviruses] wherein the structural region is from a different "type" dengue virus or flavivirus than the non-structural region." Thus, because the Lai patent does not describe a yellow fever-based chimera that includes the non-structural and capsid proteins of yellow fever virus and the pre-membrane and envelope proteins of another flavivirus, as is required by the present claims, applicants respectfully request that the rejection under § 102(e) be withdrawn. Applicants also respectfully request that the rejection under § 103(a) be withdrawn, for the same reasons discussed above in reference to the § 103(a) rejection over the Lai PCT publication.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Applicants also respectfully request that, if possible, the Examiner contact the undersigned by telephone in the event that the next Office Action in this case is not a Notice of Allowance.

Applicants also request that, effective immediately, all correspondence relating to this application be forwarded applicants' attorney at the following address:

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If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: May 12, 2003

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Version of Amendment with Markings to Show Changes Made

Claims 1, 9, and 14-16 have been amended as follows.

1. (Amended) A chimeric live, infectious, attenuated virus, comprising:

a yellow fever virus in which the nucleotide sequence encoding a prM-E protein is either deleted, truncated, or mutated so that functional yellow fever virus prM-E protein is not expressed, and

integrated into the genome of said yellow fever virus, a nucleotide sequence encoding a prM-E protein of a second, different flavivirus, so that said prM-E protein of said second flavivirus is expressed, wherein the capsid protein of said chimeric virus is from yellow fever virus.

9. (Twice Amended) A method of preventing or treating Japanese encephalitis virus [flavivirus] infection in a patient, said method comprising administering to said patient a chimeric, live, infectious, attenuated virus comprising:

a yellow fever virus in which the nucleotide sequence encoding a prM-E protein is either deleted, truncated, or mutated so that functional yellow fever virus prM-E protein is not expressed, and

integrated into the genome of said yellow fever virus, a nucleotide sequence encoding a prM-E protein of [a] Japanese encephalitis virus strain SA-14-14-2 or Japanese encephalitis virus strain Nakayama, wherein the capsid protein of said chimeric virus is from yellow fever virus [second, different flavivirus, so that said prM-E protein of said second flavivirus is expressed, wherein said second, different flavivirus corresponds to said flavivirus infection].

14. (Amended) The method of claim 9 [10], wherein the nucleotide sequence encoding the prM-E protein of said Japanese encephalitis virus [second, different flavivirus] replaces the nucleotide sequence encoding the prM-E protein of said yellow fever virus.

15. (Amended) The method of claim 9 [10], wherein said nucleotide sequence encoding said prM-E protein of said Japanese encephalitis virus [second, different flavivirus] comprises a mutation that prevents prM cleavage to produce M protein.

16. (Amended) The method of claim 9 [10], wherein the NS2B-3 protease recognition site and the signal sequences and cleavage sites at the C/prM and E/NS1 junctions are maintained in construction of said chimeric flavivirus.